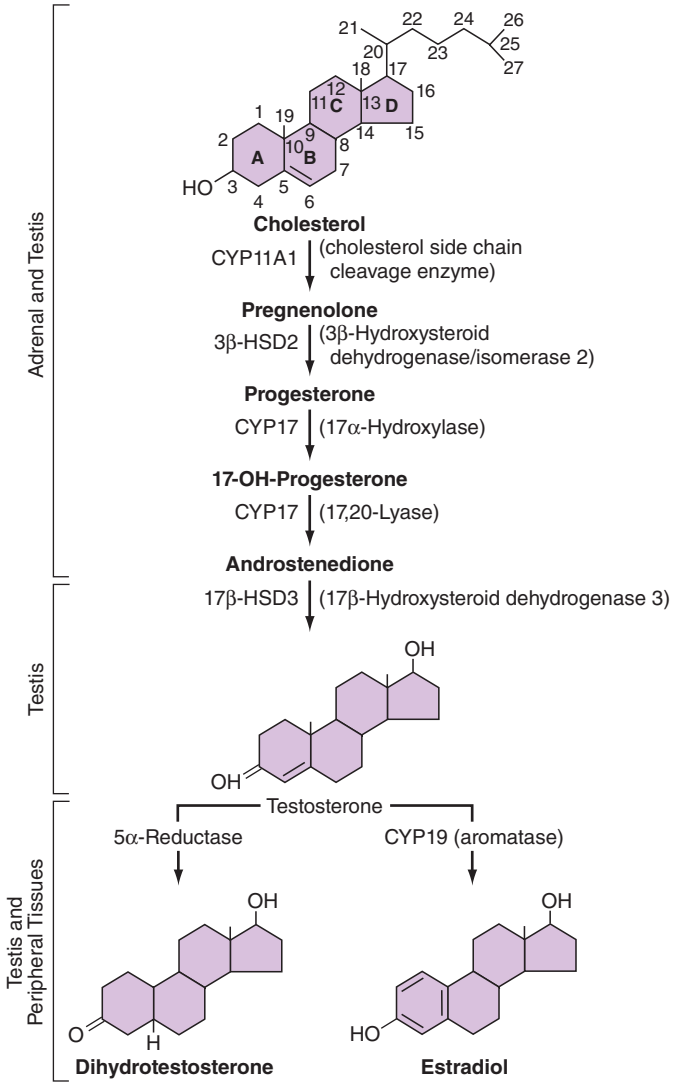

FIGURE 411-3 **The biochemical pathway** in the conversion of 27-carbon sterol cholesterol to androgens and estrogens.

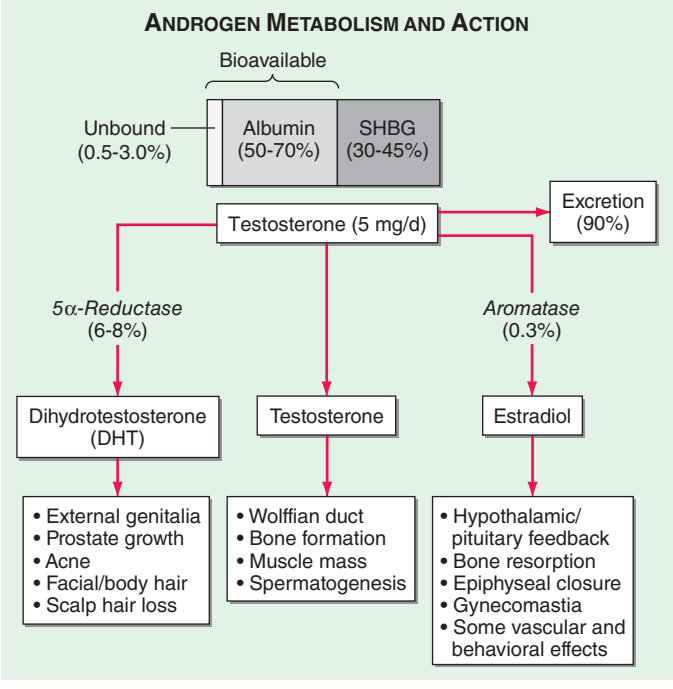

FIGURE 411-4 **Androgen metabolism and actions.** SHBG, sex hormone–binding globulin.

prostate and the skin. In the liver, testosterone is converted by a series of enzymatic steps that involve 5α- and 5β-reductases, 3α- and 3β-hydroxysteroid dehydrogenases, and 17β-hydroxysteroid dehydrogenase into androsterone, etiocholanolone, DHT, and 3-α-androstanediol. These compounds undergo glucuronidation or sulfation before being excreted by the kidneys.

Mechanism of Androgen Action Testosterone exerts some of its biologic effects by binding to androgen receptor, either directly or after its conversion to DHT by the steroid 5-α reductase. Testosterone's effects on the skeletal muscle, erythropoiesis, and bone in men do not require its obligatory conversion to DHT. However, the conversion of testosterone to DHT is necessary for the masculinization of the urogenital sinus and genital tubercle. Aromatization of testosterone to estradiol mediates additional effects of testosterone on the bone resorption, epiphyseal closure, sexual desire, vascular endothelium, and fat. DHT can also be converted in some tissues by 3-keto reductase/3β-hydroxysteroid dehydrogenase enzymes to 5α-androstane-3β,17β-diol, which is a high-affinity ligand and agonist of estrogen receptor β.

The androgen receptor (AR) is structurally related to the nuclear receptors for estrogen, glucocorticoids, and progesterone (Chap. 400e). The AR is encoded by a gene on the long arm of the X chromosome and has a molecular mass of about 110 kDa. A polymorphic region in the amino terminus of the receptor, which contains a variable number of glutamine repeats, modifies the transcriptional activity of the receptor. The AR protein is distributed in both the cytoplasm and the nucleus. The ligand binding to the AR induces conformational changes that allow the recruitment and assembly of tissue-specific cofactors and causes it to translocate into the nucleus, where it binds to DNA or other transcription factors already bound to DNA. Thus, the AR is a ligand-regulated transcription factor that regulates the expression of androgen-dependent genes in a tissue-specific manner. Some androgen effects may be mediated by nongenomic AR signal transduction pathways. Testosterone binds to AR with half the affinity of DHT. The DHT-AR complex also has greater thermostability and a slower dissociation rate than the testosterone-AR complex. However, the molecular basis for selective testosterone versus DHT actions remains incompletely explained.

THE SEMINIFEROUS TUBULES: SPERMATOGENESIS

The seminiferous tubules are convoluted, closed loops with both ends emptying into the rete testis, a network of progressively larger efferent ducts that ultimately form the epididymis (Fig. 411-2). The seminiferous tubules total about 600 m in length and comprise about two-thirds of testis volume. The walls of the tubules are formed by polarized Sertoli cells that are apposed to peritubular myoid cells. Tight junctions between Sertoli cells create a blood-testis barrier. Germ cells compose the majority of the seminiferous epithelium (~60%) and are intimately embedded within the cytoplasmic extensions of the Sertoli cells, which function as "nurse cells." Germ cells progress through characteristic stages of mitotic and meiotic divisions. A pool of type A spermatogonia serve as stem cells capable of self-renewal. Primary spermatocytes are derived from type B spermatogonia and undergo meiosis before progressing to spermatids that undergo spermiogenesis (a differentiation process involving chromatin condensation, acquisition of an acrosome, elongation of cytoplasm, and formation of a tail) and are released from Sertoli cells as mature spermatozoa. The complete differentiation process into mature sperm requires 74 days. Peristaltic-type action by peritubular myoid cells transports sperm into the efferent ducts. The spermatozoa spend an additional 21 days in the epididymis, where they undergo further maturation and capacitation. The normal adult testes produce >100 million sperm per day.

Naturally occurring mutations in the *FSHβ* gene and in the FSH receptor confirm an important, but not essential, role for this pathway in spermatogenesis. Females with these mutations are hypogonadal and infertile because ovarian follicles do not mature; males exhibit variable degrees of reduced spermatogenesis, presumably because of impaired Sertoli cell function. Because Sertoli cells produce inhibin B, an inhibitor of FSH, seminiferous tubule damage (e.g., by radiation)